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A prospective study of green tea consumption and cancer incidence, Hiroshima and Nagasaki (Japan)

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Abstract

Objectives: Laboratory and animal studies have shown a protective effect of green tea on cancer of different sites, but epidemiological evidence is limited and inconclusive. This prospective study in Japan examined the association between green tea consumption and cancer incidence.
Methods: Subjects were 38,540 people (14,873 men, mean age 52.8 years; 23,667 women, mean age 56.8 years) who responded to a mail survey carried out between 1979 and 1981. A self-administered questionnaire ascertained consumption frequency of green tea using precoded answers (never, once per day, twice to four times per day, and five or more times per day). Follow-up continued until 31 December 1994. The study analyzed solid cancers (n = 3881); hematopoietic cancers (188); cancers of all sites combined (4069); and cancer of specific sites with more than 100 cases, *i.e.* stomach (901), colon (432), rectum (193), liver (418), gallbladder (122), pancreas (122), lung (436), breast (281), and bladder (122). Poisson regression was used to allow for city, gender, age, radiation exposure, smoking status, alcohol drinking, body-mass index, education level, and calendar time.
Results: Green tea consumption was virtually unrelated to incidence of cancers under study. The relative risks of all cancers for those consuming green tea twice to four times per day and five or more times per day were 1.0 (95% confidence interval 0.91–1.1) and 0.98 (0.88–1.1), respectively, as compared with those consuming green tea once per day or less.
Conclusion: Our findings do not provide evidence that regular green tea consumption is related to reduced cancer risks.

Introduction

Tea is one of the most popular beverages in the world and is consumed by over two-thirds of the world's population [1, 2]. Tea (*Camellia sinensis*) is manufactured as black, green, or oolong tea, and green tea is primarily consumed in Asian countries, especially in China and Japan. Recent reviews on laboratory and animal studies underline the anticarcinogenic effects of polyphenols contained in green tea [2–4]. Polyphenols in green tea are (−)-epicatechin, (−)-epicatechin-3-gallate, (−)-epigallocatechin, and (−)-epigallocatechin-3-gallate (EGCG). EGCG is the major component, accounting for 40% of the total polyphenol in green tea extract, and is considered to be the most active constituent [3, 4]. Catechins, especially EGCG, have been shown to have antimutagenic, antigenotoxic, and anticarcinogenic activities [2], and also an anti-angiogenetic activity [5].

Despite evidence from laboratory studies suggesting a protective effect of green tea on cancer of different sites, data from epidemiological studies are limited and inconclusive [1]. Several case–control studies in Japan

[6–8] and China [9–11] suggested a decreased risk of stomach cancer associated with green tea drinking, but such a protective association was not reproduced in other studies [12–14]. Green tea drinking was also associated with a decreased risk of cancer of the esophagus [15], colorectum [16, 17], pancreas [17], and lung [18] in some case–control studies, but again not consistently [6, 8, 19–22].

In a cohort of atomic-bomb survivors, a mail survey was carried out in 1978–1980 to ascertain lifestyle factors, including green tea consumption, as well as smoking status, alcohol use, and educational level [23]. Among some 38,000 respondents, with mean age of 55.3 years, more than 4000 cancer cases occurred as of the end of 1994. We examined the relationship between green tea consumption and cancer incidence for all cancers as a group, and for selected types of cancer.

Materials and methods

Study subjects were members of the Life Span Study (LSS) cohort, who responded to a mail survey on lifestyle carried out between 1979 and 1981 [23]. The LSS cohort is a fixed cohort including 93,000 atomic-bomb survivors who have been under continued surveillance by the RERF since 1950 [24, 25]. The questionnaire was mailed to 55,650 of the survivors who were alive as of 1 September 1979; responses were received from 39,824 people (72%). Because the date of receipt of the questionnaire was not recorded, the start of observation period was taken as the date on which the collection of all questionnaires was completed: 1 January 1980 for men and 1 February 1981 for women. After exclusion of 1284 subjects who were found to have malignant neoplasms diagnosed before the start of the observation, 38,540 persons (14,873 men and 23,667 women) remained in the present analysis. Mean ages at the beginning of follow-up were 52.8 years in males and 56.8 years in females.

LSS mortality follow-up makes use of the nationwide family registration (*koseki*) system in Japan [25], which provides virtually complete follow-up for all cohort members residing in Japan. Incident cancer cases were ascertained by linkage to the Hiroshima and Nagasaki tumor/tissue registries [26], which have a death-certificate-only rate of less than 9% and a mortality/incidence ratio of about 50%. The observation period lasted until date of first diagnosis of any malignant neoplasm, date of death, or 31 December 1994, whichever was earliest. Table 1 shows the numbers of incident cases of primary cancers by site during the observation period. There were 3881 cases of solid cancers and 188 hematopoietic cancers, *i.e.* lymphoma, multiple myeloma, and leukemia. Analyses were done for solid cancers of selected sites with number of cases more than 100, *i.e.* stomach, colon, rectum, liver, gallbladder, pancreas, and lung. The association of green tea with breast and bladder cancers has already been examined elsewhere [27, 28], but the relevant data are presented here for comparison with other cancers.

The mail survey used a self-administered questionnaire, which included questions on consumption of 22 dietary items, smoking history, alcohol use, educational level, height and body weight, and other personal characteristics. Consumption frequency of each food/beverage item was determined from response to precoded answers; the categories for green tea were "never," "once or less per day," "twice to four times per day," and "five times or more per day."

Individual radiation dose estimates were based on the RERF Dosimetry System 1986 (DS86) [25, 29]. To allow for radiation effects on cancer incidence of selected sites, we used organ-specific DS86 weighted doses. Since DS86 does not provide doses for all organs of interest, doses for organs thought to have similar shielding were used in some cases. For solid cancers and all cancers, colon dose was used as a representative for the organs involved. Table 1 includes information on the dose used for each organ or group of organs. Since radiation dose was not of primary interest, we included those for whom DS86 estimates were not available (about 9% of the respondents) in the present analysis to make full use of the data.

For the statistical analysis, cause-specific rates were cross-tabulated by city (Hiroshima and Nagasaki), sex, age (<50, 50–59, 60–69, 70–79, and 80+ years old), calendar years (1980–1984, 1985–1989, and 1990–1994), radiation dose (0–4, 5–49, 50–199, 200–499, 500–999, 1000+ mSV, and unknown dose), smoking status (never, past, current with ≤20 cigarettes/day, and current with >20 cigarettes/day), drinking history (never, past, and current), education level (low, middle, and high), body mass index (BMI) (<19, 19–<22, 22–<25, and 25+ kg/m^2), and consumption level of green tea. Because few people (2.2% of men and 2.3% of women) reported they never drank green tea, the categories of no consumption and once or less per day were combined. Thus green tea consumption was categorized into three levels: once or less per day, twice to four times per day, and five times or more per day.

Since cancer registration was incomplete for people who had moved out of the tumor-registry catchment areas, adjustment was made to allow for the effect of migration on estimated incidence rates [30]. First, only

Table 1. Number of incident cases of primary cancers by site

Cancer site	No. of cases			
	Men	Women	Total	Organ dose
Solid cancer				
Esophagus	46	13	59	–
Stomach	518	383	901	Stomach
Colon	221	211	432	Colon
Rectum	100	93	193	Bladder
Liver	260	158	418	Liver
Gallbladder	40	82	122	Pancreas
Pancreas	43	79	122	Pancreas
Lung	265	171	436	Lung
Skin	36	53	89	–
Breast	5	276	281	Breast
Cervix uteri	–	100	100	–
Corpus uteri	–	53	53	–
Ovary	–	49	49	–
Prostate	92	–	92	–
Bladder	88	34	122	Bladder
Kidney	39	37	76	–
Thyroid gland	18	81	99	–
Other solid cancers	119	118	237	–
Subtotal	*1890*	*1991*	*3881*	Colon
Hematopoietic cancer				
Lymphoma	45	51	94	–
Multiple myeloma	20	20	40	–
Leukemia	27	25	52	–
Subtotal	*92*	*96*	*188*	Bone marrow
Total	1982	2087	4069	Colon

incident cases diagnosed in the tumor registry catchment area were included in the analysis. Second, city-, gender-, birth-cohort-, and period-specific residence probabilities were estimated on the basis of data on migration rates in the RERF Adult Health Study (AHS) cohort, a subset of the LSS cohort whose members were selected for biennial health examinations at RERF [24]. Subsequently, the migration-adjusted person-years for each cell in the person-year table were computed as the product of the total person-years in the cell and the appropriate residence probability. This adjustment reduced the effective person-years by about 15% (from 478,656 to 403,412).

Relative risks (RR) and 95% confidence intervals (CI) were estimated by Poisson regression for grouped survival data [31]. A linear excess relative risk model was used to allow for the effect of radiation exposure, with a continuous variable for known doses and an indicator variable for unknown dose [24]. The basic form of the rate model used in the analysis was:

$$\exp[\alpha_0 + \alpha_1 \ln(a) + \Sigma\beta_i x_i] \times (1 + \gamma_1 d + \gamma_2 I_{\mathrm{unk}}),$$

where α_0 and α_1 are parameters associated with the baseline rates, ln(a) is the logarithm of age, γ_1 is the slope of radiation dose response (per Sv), and γ_2 is the average excess relative risk (RR minus one) for survivors with unknown dose. β_i is a parameter corresponding to x_i, a factor that modifies the baseline risks. These included categorical variables for risk modifiers, such as city, gender, smoking status, alcohol drinking, body-mass index (BMI), education level, and calendar time. The effect of green tea consumption was assessed using categorical indicators of consumption level. The trend test was carried out using a single variable coded as 0, 1, and 2 for the lowest, intermediate, and highest levels, respectively. Interaction with radiation exposure was assessed by replacing $\gamma_1 d$ in the linear term with $\gamma_1 d \times \exp(\delta f)$, where δ is a parameter corresponding to f, an indicator variable for green tea intake. Parameter estimates and CI values were estimated using maximum-likelihood methods, and tests for trend were based on the likelihood ratio test. Computations were carried out using the Epicure software [31]. Reported p-values were two-sided, and p-values less than 0.05 were regarded as statistically significant.

Results

Table 2 presents potential confounding factors in relation to green tea consumption in males and females separately. Those at the highest level of green tea consumption were slightly older in men and women. The groups with higher green tea intake included more residents of Nagasaki than those of Hiroshima. Smoking was more frequent, and alcohol use was less frequent among men with a high consumption of green tea; smoking was less frequent at the intermediate category of green tea consumption in women. The proportion of women with middle or high education level was lower among those with a high consumption of green tea. For both men and women, BMI was the lowest among those consuming green tea twice to four times per day. There was a positive association between radiation dose and green tea consumption for women, but not for men.

Table 3 shows RRs of solid cancer, hematopoietic cancer, and cancers of all sites combined according to green tea consumption. Green tea consumption was virtually unrelated to the incidence of solid or hematopoietic cancer and cancer of all sites. Even when the group with no consumption was taken as reference, green tea intake was not associated with either all cancers or solid cancers; for solid cancers, the RRs (with 95% CI) for groups with consumption of once or less per day, twice to four times per day, and five or more times per day were 1.11 (0.88–1.4), 1.1 (0.89–1.4), and 1.1 (0.86–1.4), respectively.

Table 4 shows the association of green tea consumption with site-specific cancer incidence. Green tea consumption was not materially related to incidence for any of these cancers considered. With the lowest level of green tea consumption as reference, RRs of pancreas cancer and lung cancer were slightly, but not statistically significantly, lower than unity at the intermediate and highest consumption levels.

Consumption of green tea was weakly, but significantly positively correlated with intake of fruit and green–yellow vegetables, which were each categorized into three levels (once or less per week, twice to four times per week, and almost every day); Spearman rank correlation coefficients were 0.11 and 0.10, respectively. However, the additional adjustment for fruit and green–yellow vegetable consumption did not change the association between green tea consumption and cancers under study.

Since people may have changed their consumption pattern of green tea as well as other lifestyles due to symptoms derived from undiagnosed cancer, we repeated the analysis omitting the first 2 years of the

Table 2. Age at start of follow-up, smoking status, alcohol drinking, education level, body-mass index, and radiation dose, according to green tea consumption, by gender[a]

	Green tea consumption (times per day)			Test[b]
	0–1	2–4	5+	
Men				
Number	2172	7944	3906	
Age (years), mean ± SD	52.8 ± 14.7	52.8 ± 13.7	54.0 ± 13.2	$p < 0.001$
Residents of Nagasaki (%)	19.6	24.2	41.4	$p < 0.001$
Current smoking (%)	61.9	63.0	66.0	$p = 0.001$
Current alcohol drinking (%)	76.3	78.7	74.8	$p = 0.001$
Middle or high education level (%)[c]	51.9	52.8	53.7	$p = 0.51$
Body-mass index, mean ± SD	22.1 ± 3.1	21.9 ± 2.9	22.0 ± 2.9	$p = 0.008$
Radiation dose, mean ± SD[d]	130 ± 330	128 ± 320	132 ± 323	$p = 0.83$
Women				
Number	3243	12962	6098	
Age (years), mean ± SD	56.4 ± 14.1	56.7 ± 13.1	57.8 ± 12.7	$p < 0.001$
Residents of Nagasaki (%)	19.3	21.8	38.2	$p < 0.001$
Current smoking (%)	13.3	10.6	14.8	$p = 0.001$
Current alcohol drinking (%)	29.6	27.9	28.7	$p = 0.13$
Middle or high education level (%)[c]	53.1	54.4	51.4	$p = 0.001$
Body-mass index, mean ± SD	22.4 ± 3.5	22.2 ± 3.3	22.3 ± 3.5	$p = 0.025$
Radiation dose, mean ± SD[d]	109 ± 264	117 ± 287	135 ± 320	$p < 0.001$

[a] Missing categories were not included.
[b] One-way analysis of variance for continuous variables and chi-squared tests for categorical variables.
[c] Levels were different according to different education systems before and after World War II: high school and junior college or more for the new system, and junior high school and high school or more for the old system.
[d] Colon dose in mSv.

Table 3. Green tea consumption and risks of solid cancers, hematopoietic cancers, and all cancers combined[a]

	Consumption frequency[b] (times per day)			
	0–1	2–4	5+	Missing
Person-years	56,371	221,372	104,415	21,254
All solid cancers				
No. of cases	522	2,069	1,040	250
RR (95% CI)	1.0	1.0 (0.92–1.1)	0.98 (0.88–1.1)	0.94 (0.80–1.1)
			p-Value for trend[c] = 0.65	
Hematopoietic cancer[d]				
No. of cases	24	106	47	11
RR (95% CI)	1.00	1.2 (0.75–1.8)	0.99 (0.61–1.7)	0.75 (0.34–1.5)
			p-Value for trend = 0.81	
All cancers				
No. of cases	546	2,175	1,087	261
RR (95% CI)	1.00	1.0 (0.93–1.1)	0.98 (0.89–1.1)	0.93 (0.80–1.1)
			p-Value for trend = 0.62	

[a] Adjustment was made for city, age, gender, radiation dose, smoking status, drinking history, body-mass index, education level, and calendar time.
[b] Reference category was the lowest consumption level of green tea.
[c] Test for dose–response did not include the missing category.
[d] Lymphoma, multiple myeloma, and leukemia combined.

observation period. The results were essentially the same as described above.

We examined the association between green tea and cancer risks in the subgroup of subjects who were not exposed to radiation or received relatively low doses (less than 50 mSv), and we obtained similar results. For solid cancers the RRs (with 95% CI) for groups with consumption of twice to four times per day and five or more times per day were 1.02 (0.90–1.2) and 1.0 (0.90–1.2), respectively, compared to the group with once or less per day consumption. Furthermore, there was no measurable interaction between green tea intake and radiation exposure in the subjects as a whole.

Discussion

This large prospective study in Japan failed to find a clear, protective association between green tea consumption and the incidence of cancers of the stomach, colon, rectum, liver, gallbladder, pancreas, or lung. Similarly, no associations were seen for solid cancer, hematopoietic cancer, or cancer of all sites combined. Together with previous studies reporting null associations of green tea with breast cancer [27] and bladder cancer [28], the findings in the cohort of atomic-bomb survivors provided no affirmative evidence for a protective association of green tea drinking and cancer risk.

Several studies have addressed the relation between green tea drinking and stomach cancer risk. A total of six case–control studies have shown a lowered risk of stomach cancer associated with green tea drinking in Japan [6–8] and China [9–11], although the reported decreased risks were not always statistically significant; a dose–response trend was observed in only one study [10], and a decreased risk was noted only among individuals with a high consumption of green tea in two studies, *i.e.* ten or more cups per day [7] or seven or more cups per day [8]. Apparently conflicting to these findings are a 2-fold increased risk among drinkers compared with non-drinkers of green tea in Taiwan [13] and a RR of 1.5 for drinking two or more cups per day compared with non-daily use of green tea in Japanese men in Hawaii [14]. A case–control study in Japan found no clear association between green tea and stomach cancer risk [12]. Overall, the previous epidemiological studies seem to balance in favor of a protective association between green tea and stomach cancer. The present study, however, failed to add to evidence that green tea may have a protective effect against stomach cancer.

As for other sites of cancer, evidence is sparse regarding the association with green tea. Green tea consumption showed a significant inverse association with pancreatic cancer in China [17], but a significant positive association in Japan [21]. Two case–control studies of lung cancer also showed conflicting findings as to the association with green tea [18, 22]. Of four case–control studies examining the relation between green tea and esophageal cancer, one in China showed a clear,

Table 4. Risk of site-specific cancer incidence according to green tea consumption[a]

Site of cancer	Consumption frequency[b] (times per day)			p-Value for trend
	0–1	2–4	5+	
Stomach				
No. of cases	123	480	233	
RR (95% CI)	1.0	1.0 (0.82–1.2)	0.95 (0.76–1.2)	0.56
Colon				
No. of cases	57	231	124	
RR (95% CI)	1.0	1.0 (0.76–1.4)	1.0 (0.76–1.4)	0.79
Rectum				
No. of cases	22	107	55	
RR (95% CI)	1.0	1.3 (0.80–2.0)	1.3 (0.77–2.1)	0.64
Liver				
No. of cases	58	230	103	
RR (95% CI)	1.0	1.1 (0.80–1.4)	0.95 (0.69–1.3)	0.46
Gallbladder				
No. of cases	16	61	39	
RR (95% CI)	1.0	0.9 (0.57–1.7)	1.2 (0.66–2.2)	0.74
Pancreas				
No. of cases	19	60	31	
RR (95% CI)	1.0	0.8 (0.51–1.4)	0.79 (0.45–1.4)	0.48
Lung				
No. of cases	67	205	123	
RR (95% CI)	1.0	0.78 (0.60–1.0)	0.79 (0.59–1.1)	0.21
Breast				
No. of cases	34	170	66	
RR (95% CI)	1.0	1.2 (0.86–1.8)	1.0 (0.67–1.6)	0.80
Bladder				
No. of cases	15	62	35	
RR (95% CI)	1.0	1.1 (0.62–2.0)	1.1 (0.61–2.1)	0.77

[a] Adjustment was made for city, age, gender, radiation exposure, smoking status, alcohol drinking, body-mass index, education level, and calendar time.
[b] Reference category was the lowest level of green tea consumption; data for the missing category were not shown.

inverse association with risk in women [15]; another in China reported a significant positive association [20]; and two studies found no measurable association in Singapore [19] and Japan [8]. The inconsistency in these findings regarding esophageal cancer may pertain to possible confounding due to drinking tea and other fluids at high temperatures [32]. Interestingly, in a case–control study in China [15], green tea drinking was associated with an increased risk of esophageal cancer among men and women consuming burning-hot fluids, but was inversely related to the risk among non-consumers of burning-hot fluids.

Prostate cancer is among the most common cancers for men in Europe, North America, and Australia [33]. In contrast, the Japanese and Chinese population, which traditionally consume several cups of green tea, have one of the lowest rates of prostate cancer in the world. Many *in-vitro* and *in-vivo* experiments have suggested a potential anticarcinogenic effect of green tea in the prostate [34]. We did not examine the relation between green tea and prostate cancer in the present study because of the relatively small number of prostate cancer cases.

Green tea consumption was weakly, positively correlated with fruit and green–yellow vegetable consumption in the present study. Fruit and vegetable consumption have been shown to be associated with a decreased risk of different cancers [35], and may confound any protective association between green tea and cancer. While the adjustment for fruit and green–yellow vegetables did not alter the association with green tea in the present study, some studies have found an inverse association of green tea with stomach cancer [10], esophageal cancer [15], and all cancers combined [36], after adjustment for both fruit and vegetables.

Our failure to find a clear, protective association between green tea and cancer may be due to some crudeness in the assessment of green tea intake; green tea consumption was determined only in terms of self-reported daily frequency of drinking, and the highest category was five or more cups per day. Bioactivity of a cup of green tea obviously differs by the amount of green tea leaves used to brew it and the frequency of renewing a tea batch in the pot. In five case–control studies in China, green tea consumption was assessed in terms of the amount of green tea leaves consumed in a given period [10, 11, 15, 17, 20]. Four of them reported a decreased risk of stomach cancer [10, 11], colorectal cancer [17], esophageal cancer [15], and pancreatic cancer [17] associated with green tea. Interestingly, in Shizuoka prefecture, which has the highest production of green tea leaves in Japan, residents of towns with low mortality from stomach cancer were found not only to drink green tea more frequently, but also to renew tea leaves more frequently than those of a town with high mortality from stomach cancer [37].

While drinking green tea five times per day or more frequently implies a consumption of at least five cups per day, the category may have been too broad to detect a protective association with a heavy use of green tea. In previous studies [7, 18, 35], those drinking over ten cups per day of green tea accounted for approximately 10–15%. A significant decrease in the risk of stomach cancer was found only for the highest consumption levels such as ten cups or more per day [7] and seven cups or more per day [8]. Likewise, appreciable decreases in the risk of lung cancer [18] and mortality from cancer of all sites combined [36] were reported only among those drinking ten cups or more of green tea per day. These findings suggest that it may require a fairly large amount for green tea to exert a protective effect against cancer. The amount of ten cups of green tea per day was comparable to the concentration of green tea extract used in animal experiments that showed a protective effect in both gastric and colorectal carcinogenesis [38]. However, there still remains the possibility that an even lower consumption of green tea may be related to decreased cancer risk. Although we found no difference in the risk between those consuming green tea once or less per day and non-green tea drinkers, this may have been due to the limited number of non-green tea drinkers.

The study population was unique in that most of the subjects had been exposed to ionizing radiation, which has been shown to be significantly related to overall and specific cancer risks in the LSS cohort [24]. However, the present findings would be generalizable to other populations with no radiation exposure, since similar results were noted among individuals with no or relatively low radiation exposure, and since there was no evident interaction between green tea intake and radiation exposure.

This study is the only large-scale prospective study of green tea consumption and cancer. There were a large number of cancer cases, and green tea consumption varied considerably among individuals in the cohort. Because of its prospective nature, this study is free from recall and selection biases that might affect the results of case–control studies. Because cancer incidence was not ascertained among migrants out of the catchment area, adjustment was made for the denominators as regards city, gender, birth-cohort, and calendar period. If the migration was differential in terms of green tea consumption, the relation between green tea and cancer could be biased in either direction. It is, however, unlikely that such a differential emigration occurred to such an extent, that any protective associations were totally masked. While our findings do not preclude the possibility of protective effects of consuming high levels of green tea, they do not support the hypothesis that modest levels of regular green tea consumption provide significant protection against cancer risks.

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